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March 8, 1999

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APPLICATION NUMBER: 09/031,858

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PCT APPLICATION NUMBER: PCT/US99/04158

## PRIORITY DOCUMENT

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APPLICATION  
FOR  
UNITED STATES LETTER PATENT

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Barry S. Fogel

TO THE ASSISTANT COMMISSIONER FOR PATENTS:

BE IT KNOWN, that I, Barry S. Fogel have invented certain new and useful improvements in  
METHOD FOR TREATING PAINFUL CONDITIONS OF THE ANAL REGION AND  
COMPOSITIONS THEREFOR of which the following is a specification:

# Method for Treating Painful Conditions of the Anal Region and Compositions Therefor

## Background of the Invention

This invention relates to methods and compositions for treating painful conditions of the anal region and more particularly for treating anal fissures, thrombosed or inflamed hemorrhoids, for pain associated with ligation of internal hemorrhoids and for chronic anal pain.

Anal fissures can be an extremely painful condition. The primary reason for severe pain is spasm of the anal sphincter. This spasm causes ischemia, which both produces pain and interferes with healing (Sharp, American Journal of Surgery, 1996; Volume 171, pages 512-515; Schouten et al., 1993, Scandinavian Journal of Gastroenterology, Volume 31, Supplement 218, pp. 78-81). Spasm of the anal sphincter also plays a role in the pain of inflammatory conditions of the anal region, such as inflamed or recently thrombosed hemorrhoids (Janicke & Pundt, 1996, Emergency Medicine Clinics of North America, Volume 14, pp. 757-788). See also, Madoff, RD., "Pharmacologic Therapy for Anal Fissure," New England Journal of Medicine 1998 Jan 22:338(4) 217-20.

Effective treatments for anal fissures, whether medical or surgical, involve relaxation of the spastic muscle. These treatments include lateral sphincterotomy, injection of the sphincter with botulinum toxin, and application of nitroglycerin ointment. A recent review by Sharp of treatment for chronic anal fissures recommends beginning with nitroglycerin ointment. If the fissure has not healed in six weeks, botulinum toxin injections are given. That review notes that "considerable educational effort is required to successfully adjust the dose" of nitroglycerin (Sharp, 1996, *ibid.*). It states that nitroglycerin "will often eliminate the severe pain of fissure-in-ano in 1 day". Schouten et al. (1993, *ibid.*) used topical isosorbide dinitrate to treat chronic anal fissures, attaining pain relief within 10 days". Lund & Scholefield (1997, *Lancet*, Volume 349, pp. 11-14) reported a randomized controlled trial of 0.2% nitroglycerin ointment for anal fissure. At 2 weeks, pain on defecation, as measured by a visual analogue scale (0=no pain,

- (X) the specification filed herewith  
( ) U.S. Patent Application Serial Number \_\_\_\_\_  
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If the rights of the above-identified small business concern are not exclusive, each individual, concern, or organization having rights to the invention is listed below\* and no rights to the invention are held by any person, other than the inventor(s), who could not qualify as a small business concern under 37 CFR 1.9(d) or a non-profit organization under 37 CFR 1.9(e).

\*NOTE: Separate verified statements are required from each named person, concern, or organization having rights to the invention, averring to their status as small entities. (37 CFR 1.27).

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(X) INDIVIDUAL ( ) SMALL BUSINESS CONCERN ( ) NON-PROFIT ORGANIZATION

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I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))


I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

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DATE

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has not been reported as a treatment for anal fissures. Sucralfate, when applied to a damaged mucosa, forms an adherent film that protects the mucosa and promotes healing (Kochhar et al., 1990; Diseases of the Colon and Rectum, Volume 33, pp. 49-51). In addition, sucralfate lowers local levels of the inflammatory mediator PGE<sub>2</sub> (Zahavi et al., 1989; Diseases of Colon and Rectum, Volume 32, pp. 95-98).

### Summary of the Invention

One aspect of the invention is a composition comprising a combination of nitroglycerin and sucralfate. Yet another aspect is a composition comprising a combination of nitroglycerin, lidocaine and sucralfate. These compositions may be combined in a petrolatum base along with a water soluble lubricant such as K-Y<sup>TM</sup> Jelly. These compositions have analgesic properties.

Another aspect of the invention is a method for treating a painful condition on a body portion which includes providing a composition of nitroglycerin and sucralfate and applying the composition to the body. The composition may also include lidocaine. The compositions may further be mixed with an ointment base such as petrolatum and a water soluble lubricant. These ointments are particularly effective in treating painful conditions of the anal region by applying the composition to the anal region. Painful conditions which respond to the treatment of the invention include anal fissures, thrombosed or inflamed hemorrhoids, pain resulting from ligation of internal hemorrhoids and other chronic anal pain. A suitable water soluble lubricant is K-Y<sup>TM</sup> Jelly.

### Description of the Preferred Embodiment

As discussed above, nitroglycerin alone and lidocaine alone have been proposed as a treatment for painful conditions in the anal area. The local anesthetic effect of lidocaine is based on a different mechanism of action than the analgesic effect of nitroglycerin. For this reason, I thought these two compounds might have additive or synergistic actions in the treatment of pain of anal fissures and other painful conditions in the anal region. I further reasoned that sucralfate might keep the other two ingredients adherent to the fissure, prolonging their action. Furthermore, the adherent film produced

by sucralfate might protect the raw area from irritation by the fecal stream. With these considerations in mind, I prepared a composition which was the combination of nitroglycerin and sucralfate. This formula was 60 grams of K-Y™ Jelly, 15 grams of 2% nitroglycerin ointment, and 6 grams of sucralfate. I prepared a second composition of  
5 nitroglycerin, lidocaine and sucralfate in a base of petrolatum and a water soluble lubricant. The formulation was 240 grams petrolatum, 180 grams of K-Y™ Jelly, 60 grams of 2% nitroglycerin ointment, 30 grams of sucralfate and 9.6 grams lidocaine base. The amount of nitroglycerin may be in the range of 30-60 grams. The sucralfate was in powder form.

10       **Case 1:** A 49 year old man had a chronic anal fissure, which had persisted for several months, producing chronic rectal pain relieved only by narcotic analgesics. Anoscopy, performed separately by a rectal surgeon and a gastroenterologist, confirmed the presence of a moderately large anal fissure. The surgeon thought that surgery was necessary, and the gastroenterologist proposed cauterization. Neither felt that the fissure  
15 would heal without invasive treatment of some kind.

The patient was first treated with nitroglycerin cream, 0.5%. (The cream was prepared by diluting 2% nitroglycerin ointment with a K-Y™ Jelly. This gave substantial but not complete pain relief that lasted about 2 hours, after which the pain gradually returned. Over several weeks, pain was relieved every time the cream was  
20 applied, but returned if it was stopped. He was then switched to the combination of nitroglycerin and sucralfate. With this combination, relief lasted 3-4 hours at first, and then lasted longer and longer with repeated applications. Within two weeks, he had full relief applying the cream only twice a day. Within six weeks, the symptoms were totally relieved and the analgesic cream was no longer necessary.

25       **Subsequent Cases:** 4 subsequent patients, all but one with anoscopically confirmed anal fissures, were treated with the combination of nitroglycerin, lidocaine, and sucralfate, with the expectation of even better relief. (Patient #4 suffered from chronic anal pain of unknown cause.) All 4 of those treated obtained relief, and all chose to continue the medication for several days. Patients were instructed to use the cream as

often as they needed for pain relief they found satisfactory. The following table summarizes these patients' reports of their experience with the analgesic cream:

	Patient: Sex and age	1: ♀ 47	2: ♀ 37	3: ♂ 69	4: ♂ 54 (chronic anal pain)
	Duration of pain before treatment	1 week	2 weeks	5 weeks	2 years of discomfort, 5 months of pain
5	Other treatment tried	None	Generic hemorrhoid cream	Anusol™, Nupercainal™, sitz baths	None
	Time from application to relief	30 minutes	5 minutes	30 minutes	5-10 minutes
	Percentage of pain remaining after application of the cream	25%	50%	50%	No pain
	Times a day applied	2	2-3	2	2
10	Persistence of benefit	Yes	Yes	Yes	Yes
	Resolution of painful condition	Yes	Yes	Yes	Partial
	Time to resolution of condition	2 weeks	1 week	1 week	Severe pain resolved in 1 week
	Side effects	Headache	Headache, burning sensation	None	Burning sensation
15	Stopped medication because of side effects	No	No	No	No
	Persistence of side effects	No	Yes	N/A	No

Five patients, all with anoscopically confirmed fissures, received jars of the analgesic cream, and were instructed to apply it as needed to eliminate their pain. All got complete relief within minutes. The complete relief they obtained contrasted with the partial relief usually reported by patients treated with nitroglycerin ointment alone. Applications about four times daily were adequate to completely control their pain. Three of the patients had been scheduled for surgery to treat their fissures. They had been given the cream 3 to 4 weeks before the date planned for the operation. All three patients cancelled their operations, because they had had sufficient pain relief. One underwent repeat anoscopy, which revealed complete healing of the fissure.

None of the 5 patients required any oral analgesics, sitz baths, or other treatments to relieve pain, as soon as they had access to the nitroglycerin-lidocaine-sucralfate cream.

An additional experiment was performed to establish the effect of the sucralfate. A 64 year old man with severe pain following the rubber band ligation of a hemorrhoid was treated. He had had six weeks of pain prior to the treatment. We treated him on

alternate days with either the composition including nitroglycerin, lidocaine and sucralfate or the composition without the sucralfate. He was instructed to reapply the formula any time the pain began to recur. The three ingredient formula gave 90% relief (i.e., pain reduced to 10% of baseline) within fifteen minutes. The patient applied the cream three more times during the next twenty-four hours obtaining satisfactory relief.

The formulation without sucralfate gave less relief, and the pain recurred sooner. The patient applied the two-ingredient (without sucralfate) formula a total of five more times during the next twenty-four hours. Not only did the three-ingredient (with sucralfate) formula act faster, but it was associated with a less severe headache than the two-ingredient formula. The two-ingredient formula may have caused a worse headache because the patient might have used more of it to get relief. Alternatively, the sucralfate in the three-ingredient formula may have slowed the systemic absorption of nitroglycerin.

An additional three patients were treated with various formulations to establish the benefit of sucralfate and to illustrate that the concentration of nitroglycerin needed to treat anal fissure can be lower than that reported in the literature. These cases also show that adding nitroglycerin to the sucralfate-lidocaine combination improves efficacy. The three additional cases are shown in the table below:

Patient: Sex and age	1: ♀ 68	2: ♂ 81	3: ♂ 33
Diagnosis	Anal fissure	Anal fissure	Inflamed hemorrhoid
Duration of pain before treatment	6 months	3 months	2 months
Other treatment tried	None	Sitz baths, suppositories; cortisone cream	Desitin ointment
Time from application to relief	30 minutes	15 minutes	5 minutes
Percentage of pain remaining after application of the cream	25%	70% after first application; almost none after 4 weeks	Complete relief
Times a day applied	5	2-3	3-4
Persistence of benefit	Yes	Yes	Yes
Resolution of painful condition	Yes	Yes	Yes, but it recurs occasionally
Time to resolution of condition	Not known	4 weeks	Not known
Side effects	None	None	No
Stopped medication because of side effects	No	No	No
Persistence of side effects	N/A	N/A	N/A



Patient #1 received the nitroglycerin-lidocaine-sucralfate formula discussed above (formula A) and a formulation without sucralfate (formula B) in the sequence A-B-A over three days. The reported benefit shown in the table above resulted from use of formula A. Formula B was not tolerated; it produced a throbbing headache. This case suggests that sucralfate may actually provide some protection against nitroglycerin-induced headache, perhaps by influencing the absorption of the nitroglycerin.

Patient #2 in the table above received a modified formula with 30 grams of 2% nitroglycerin ointment per 500 grams of the nitroglycerin-lidocaine-sucralfate mixture. The concentration of nitroglycerin in this mixture -- 0.12% -- was lower than the 0.2% concentration reported in recent randomized controlled trials of the use of nitroglycerin as a single agent. Nonetheless, the mixture was efficacious and did not cause headaches (or any other side effects). This case supports the inventor's premise that nitroglycerin in combination with sucralfate and lidocaine is superior to nitroglycerin alone. The combination is efficacious at lower doses of nitroglycerin and the combination is less likely to cause headache.

Patient #3 received formula A and a formulation without nitroglycerin (formula C) in the sequence A-C-A over three days. This formula C (without nitroglycerin) did not give complete relief; the patient estimated that 25% of the pain remained after application. This case supports the relevance of nitroglycerin to the analgesic activity of the mixture, even in conditions other than anal fissure, where the efficacy of nitroglycerin is well established.

Conclusions: A topical analgesic cream or ointment for anal fissures that contains nitroglycerin will be more efficacious if it also contains sucralfate. A cream or ointment containing nitroglycerin, sucralfate, and lidocaine is especially efficacious.

Other anal and rectal conditions, such as inflamed hemorrhoids, produce pain for the same reasons as an anal fissure -- a combination of inflammation and spasm of the anal sphincter. Therefore, the combination cream or ointment is expected to be similarly helpful for the pain of those conditions (as demonstrated in patient #3 in the table above). The cream or ointment may also provide relief for pain following rubber band ligation of internal hemorrhoids, as this procedure often leads to sphincter spasm and local



1. Composition comprising a combination of nitroglycerin and sucralfate.
2. Composition comprising a combination of nitroglycerin, lidocaine and sucralfate.
3. The composition of claims 1 or 2 wherein the combination is in a petrolatum base.
4. The composition of claim 3 further including a water soluble lubricant.
5. Analgesic composition comprising:  
nitroglycerin and sucralfate in an ointment or cream base.
6. Analgesic composition comprising:  
nitroglycerin, lidocaine and sucralfate in an ointment or cream base.
7. The analgesic composition of claims 5 or 6 wherein the ointment or cream base comprises petrolatum and a water soluble lubricant.
8. Method for treating a painful condition on a body comprising:  
providing a composition of nitroglycerin and sucralfate; and  
applying the composition to the body.
9. Method for treating a painful condition on a body comprising:  
providing a composition of nitroglycerin, lidocaine and sucralfate; and  
applying the composition to the body.
10. Method of claims 8 or 9 wherein the providing further includes mixing the composition in an ointment or cream base.
11. Method of claim 10 wherein the ointment or cream base comprises petrolatum and a water soluble lubricant.
12. Method for treating painful conditions of the anal region comprising:  
providing a composition of nitroglycerin and sucralfate; and  
applying the composition to the anal region.
13. Method for treating painful conditions of the anal region comprising:  
providing a composition of nitroglycerin, lidocaine and sucralfate; and  
applying the composition to the anal region.
14. The method of claims 12 or 13 wherein the composition includes an ointment or cream base.

15. The method of claim 14 wherein the ointment or cream base comprises petrolatum and a water soluble lubricant.

16. The method of claims 12 or 13 wherein the painful condition is an anal fissure.

5 17. The method of claims 12 or 13 wherein the painful condition is thrombosed or inflamed hemorrhoids.

18. The method of claims 12 or 13 wherein the painful condition results from ligation of internal hemorrhoids.

10 19. Method for treating a painful condition of the anal region comprising:  
providing a composition of nitroglycerin, lidocaine and sucralfate in a base of petrolatum and a water soluble lubricant; and  
applying the composition to the anal region.

20. The method of claim 19 wherein the composition comprises approximately 240 grams petrolatum, 180 grams of lubricant, 60 grams 2% nitroglycerin,  
15 30 grams sucralfate and 9.6 grams lidocaine.

21. The method of claim 20 wherein the lubricant is K-Y™ jelly.

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## COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

### METHOD FOR TREATING PAINFUL CONDITIONS OF THE ANAL REGION AND COMPOSITIONS THEREFOR

the specification of which (I authorize Choate, Hall & Stewart to check one of the following, three choices, and fill in the blanks, if applicable):

  X   is attached hereto

       was filed on                      as Application  
Serial No.                      and amended on                      (if  
applicable).

       was filed as PCT international application No.                     ,  
on                      and was amended under PCT Article 19  
on                      (if applicable).

I hereby state that I have reviewed and understood the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledged the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s):

Priority Claimed

<u>      </u> (Number)	<u>      </u> (Country)	<u>      </u> (Day/Month/Year/Filed)	<u>  </u> Yes	<u>  </u> No
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<u>      </u> (Number)	<u>      </u> (Country)	<u>      </u> (Day/Month/Year/Filed)	<u>  </u> Yes	<u>  </u> No
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I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or PCT international application(s) designating the United States of America listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

_____ (Application Serial No.)	_____ (filing date)	_____ (status-patented, pending, abandoned)
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_____ (Application Serial No.)	_____ (filing date)	_____ (status-patented, pending, abandoned)
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PCT Applications designating the United States:

_____ (PCT Appl. No.)	_____ (U.S.S.N.)	_____ (status-patented, pending, abandoned)
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I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national filing date of this application.

Provisional Application(s):

_____ Application Number	_____ Filing Date	_____ Status
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I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:  
Sam Pasternack, Reg. No. 29,576; David J. Powsner, Reg. No. 31,868; Mary Rose Scozzafava, Reg. No. 36,268; Mary Raynor Jimenez, Reg. No. 37,219; Brenda Herschbach Jarrell, Reg. No. 39,223; Douglas D. Robinow, Reg. No. 40,787 and Kevin M. Tormey, Reg. No. 41,351.

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[illegible]





- (X) the specification filed herewith  
( ) U.S. Patent Application Serial Number \_\_\_\_\_  
filed \_\_\_\_\_  
( ) U.S. Patent Number \_\_\_\_\_  
issued \_\_\_\_\_

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\*NOTE: Separate verified statements are required from each named person, concern, or organization having rights to the invention, averring to their status as small entities. (37 CFR 1.27).

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DATE

2/25/98